Application No: 10/630,348
Examiner: MERCIER, MELISA S

REMARKS

Applicant has amended claims 1, 3-5, 7-14, 15-17, 21, 23, 28, 33-35, 37-44, 45-47, 52 and 53. The claims were amended to make the subject matter of the claimed invention clearer and to overcome the Examiner's rejections and objections. No new matter was added to the claims.

The Examiner has objected to claims 10 and 21 as being in impermissible multiply dependent form. As such, Applicant has amended claims 10 and 21 to be dependent in the alternative so as to comply with 37 C.F.R. 1.75(c). Therefore, the Examiner's objections have been rendered moot.

The Examiner has rejected claims 3-5, 7-9, 11-13, 15-17, 28, 33-35, 41 and 47 under 35 U.S.C. § 112, second paragraph for being indefinite.

Claims 3, 11, 33 and 41 have been amended by deleting the phrase "such as". Claim 4 and 34 have been amended to replace the phrase "selected preferably from" with "selected from". Claims 5, 28, 35 and 47 have been amended to include the generic terminology. Claims 7-9 and 15-16 have been amended by deleting the phrases "preferably, more preferably, and most preferably".

With respect to claim 12, Applicant points out that claim 11 has been amended to clarify what "hydrophobic release controlling agents" the Applicant is referring to in claim 12 and 13. With respect to claim 13, Applicant has amended claim 13 to include fatty acid esters as hydrophobic release controlling agents in order to provide clarity. Claim 17 has been amended by deleting the phrase "and the like".

The Examiner has rejected claims 1-3, 6-11, 14-27, 29-33, 36-41 44-46, and 48-60 under 35 U.S.C.§103(a) as unpatentable over Santus et al. (U.S.P.N. 5,472,704, herein Santus).

Claim 1 points out non-obvious subject matter because it recites a modified dual retard controlled release dosage form for high solubility drugs. Additionally, claims 30, 31

and 60 also point out non-obvious subject matter because they too recite a dual retard controlled release dosage form for high solubility drugs. They merely recite the claimed subject matter with specific compositions or processes.

Applicant points out that many of the prior art modified delivery systems utilizing matrix dosage forms provide useful levels of control to the delivery of sparingly soluble drugs. However, and particularly for highly soluble drugs, such a matrix does not provide adequate control over the release rate. Instead, they result in a release that approximates first-order kinetics and have a problem with dose dumping or burst release. However, since many modified release dosage forms contain comparatively large amounts of highly soluble active ingredients it is often necessary to include large amounts of suitable excipients in order to achieve appropriate controlled release profiles. Clearly, this will tend to increase the size of the dosage form. The present invention rectifies some of these issues found in the prior art. As such, the amended claims point out non-obviousness subject matter by reciting a technique which can effectively control the release of the highly soluble active ingredient as well as having a small size.

Santus is limited for use in controlled release compositions to provide a sustained release for the drugs having limited drug solubility (gastric / enteral), small absorption rate constant or the presence of "windows" of absorption (i.e. a limited time of absorption which stops upon saturation) or to release the drug at the site of absorption such as nasal cavity, rectal cavity or colon. Santus describes bioadheasives as one of the important characteristics in a pharmaceutical composition. It is also disclosed by Santus that the bioadheasive controlled-release microunits are inclined to adhere to one another and may therefore be additionally treated with hydrophobic agents, including steric acid, magnesium stearate, calcium stearate, zinc stearate, talc, glyceryl fumarate, hydrogenated vegetable oils, and polyethylene glycols (column 7, lines 30-35). These controlled release bioadhesive micro units are treated with the above mentioned hydrophobic agents in order to provide protective coating so as to avoid clump formation.

Santus discloses that the release of a very soluble active ingredient can be slowed down to the desired rate by using a hydrophobic matrix as the release controlling component (Column 5, lines 29-32). However, Santus discloses following four techniques for preparation of sustained release compositions (Column 4, lines: 35-42).

1. reservoir units
2. matrix units
3. osmotic units
4. biodegradable units

Hence Santus does teach, in a very general manner, the use of hydrophobic release components for making controlled release formulations of highly soluble drugs. However, Santus fails to point the use of microunits for the controlled release of an active ingredient obtained singly from reservoir or matrix or osmotic or biodegradable units. Even if Santus did disclose the use of microunits for the controlled release of an active ingredient, which Applicant does not concede, there is insufficient disclosure to render the subject matter of the amended claims obvious. Moreover, Santus discloses that the preparation of controlled release microunits in use of matrix units is more complex than that of reservoir units (Column 4, lines 60-61). Thus, Santus teaches away from a dual retard technique and discloses a preference for using the reservoir system.

It is important to note that in Santus the embodiments and examples only disclose matrix systems using melt granulation and large amounts of the release controlling agent with the active ingredient (See Example 1a/1b, API: Rate controlling polymer is 1≤1). Therefore, it is clear that Santus discloses various bioadhesive polymers and doesn't disclose the use of ammonio methacrylate copolymers or fatty acid esters.

A further illustration of the differences between the amended claims and the cited prior art can be found in Example 1 of Santus (Col 8-9). Santus points out the use of a hydrophobic matrix to control the release of Furosemide (BCS, Class IV drug) using a

large amount of release controlling agent. Furosemide, being insoluble drug, requires such a large amount of release controlling agent in order to obtain the desired release profile without having a burst release or dose dumping. If a person skilled in the art uses this technique for highly soluble drugs, such as the ones pointed out in the amended claims, it will require a still larger amount of release controlling agent to achieve the similar release profile. This will ultimately increase the size of formulation. This is in marked contrast to the effect of the dual retard technique pointed out in the amended claims. The techniques recited in the amended claims significantly reduce the burst effect and effectively control the release rate of high solubility active ingredients for prolonged periods using much less quantities of release controlling agent and other excipients. This is demonstrated in figures 2, 3, and 4 of the instant application. Furthermore, figures 2-4 clearly show that when release rates of formulations containing the same quantity of hydrophobic release controlling agents were manufactured by dual retard techniques and with simple wet granulation, as in Santus, the formulations with dual retard technique significantly reduced the burst effect and controlled the release rate of a high solubility active ingredient for a prolonged period.

Lastly, the prior art specifically teaches away from techniques used in the amended claims. In Santus, the method of the spray coating microunits is discouraged. (Col. 7, lines 55-67) The Applicants invention clearly points out spray coating of micro matrix particles. (Page 4, paragraph 56, line 24-30).

In light of the foregoing, it is clear that those skilled in the art would not find the amended claims obvious in light of Santus. Santus teaches, directs and motivates a one skilled in the art to preferentially use reservoir units and melt granulation for preparation of sustained release composition for highly soluble drugs and also teaches the use of large quantities of excipients. These procedures applied to a highly soluble drug will lead to larger dosage forms. This is in marked contrast to the present invention which requires less controlling agent and does not suffer from burst release.

Considering the above, it is clear that to derive the instant invention (dual retard composition) a person having ordinary skill in the art would need to engage in significant undue experimentation and modifications beyond merely altering the active agent to polymer ratio. Such modifications would clearly not be obvious in light of the disclosures made in Santus. Therefore, Applicant respectfully submits that the amended claims are not obvious in light of Santus.

The Examiner has rejected claims 4, 5, 12, 13, 28, 34, 35, 42, 43, and 47 under 35 U.S.C. §103(a) as being obvious in view of Santus et. al (U.S.P.N 5,472,704), in further view of Akiyama et. al (U.S.P.N. 5,399,357, herein Akiyama).

Applicant respectfully submits that the above rejected claims are all dependent on claims 1, 30 or 31. Applicant has provided amendments and arguments that render the Examiner's rejections with respect to the independent claims moot. Therefore the above rejected claims can not be obvious since they depend from non-obvious independent claims. However, Applicant respectfully disagrees that the above cited claims are obvious and provides arguments that render the Examiner's rejection moot.

Akiyama is limited to disclosing a sustained release composition comprising a matrix preparation comprising a pharmaceutically active ingredient dispersed in a matrix of fatty acid ester of polyglycerol, such as hydrogenated castor oil (Col. 4, lines 9-11). The micromatrix system, according to Akiyama is manufactured by melting fatty acid ester of polyglycerol and adding the active ingredient and other ingredients into a molten mass, which is then converted into granules by spray cooling (Col 6, lines 30-65). This micromatrix system is ultimately responsible for the controlled release of active ingredients. These granules may be coated for reforming their surfaces, masking their taste, or giving them solubility in the intestine. (Col. 7 lines 6-10).

The process disclosed in the amended claims are entirely different from the subject matter disclosed by Akiyama. The amended claims recite an active agent and one or more hydrophobic release controlling agents that are mixed and granulated by adding a solvent.

Akiyama is limited to a fatty acid ester of polyglycerol being melted and the addition of the active agent.

Furthermore, in the amended claims, the micro matrix particles are further coated with rate controlling agents, whereas in Akiyama the coating of granules is done to reform their surfaces, mask their taste, or give them solubility in the intestine. Akiyama doesn't teach that the release can be controlled by coating of micromatrix granules. Hence the processes of preparing micromatrix particles as recited in in the amended claims are different than the process pointed out in Akiyama. Akiyama also fails to point out the coating of micro matrix particles in order to control release.

Also note that Akiyama, as disclosed in all the examples (1-30), uses large amounts of fatty acid ester of polyglycerol (release controlling agent) to obtain desired release profile without having any burst release or dose dumping. Much like Santus, this will ultimately increase the size of the formulation. Contrary to both Akiyama and Santus, the amended claims recite dual retard techniques which enable the size of the dosage form to be reduced considerably.

Akiyama doesn't provide any teaching to prepare dual retard sustained release formulations, and as such, combining it with Santus would fail to teach all the elements of the amended claims. Furthermore, any combination of Akiyama and Santus would require undue experimentation to attain the similar results as found in the present invention. At best, any resulting combination would result in a large dosage form containing a fatty acid ester. More importantly, the dual retard technique of the amended claims can not be found anywhere in the cited prior art references. Moreover, Methacrylic Acid – Methyl Methacrylate Copolymers (EUDRAGIT L100-55®, EUDRAGIT L-100®, EUDRAGIT S-100®) used in Akiyama as mentioned in the description (Col. 6 lines 3-5, Col. 5; Col 5, lines 66-68) is known for enteric protection. Also, use of ammonio methacrylate copolymers is not disclosed by Akiyama. According to USP-NF, Ammonio Methacrylate Copolymer (ammonio Methacrylate Copolymer –ph. Eur.) and Methacrylic Acid

Copolymers (Methacrylic Acid – Mrthyl Methacrylate Coplymers; Ph. Eur) have different monographs, different structures, different chemistry and are used for different purposes. Therefore, Akiyama, alone or combined with the teaching of Santus, fails to teach a person skilled in the art the dual retard technique for high soluble and high dose drugs as recited in the amended claims.

Additionally, the combined teaching of Santus and Akiyama would teach away from the non-obvious subject matter found in the amended claims. The combined prior art teaches the use of large amounts of excipients and polymers, which will lead to unacceptably large dosages, particularly for high soluble and high dose drugs such as metformin. Finally, both prior art references themselves teach cumbersome techniques such as slugging and melt granulation which are not used in the amended claims and are not equivalent to the techniques recited.

Applicant notes the Examiner's provisional rejection under 35 U.S.C. 101 in light of co-pending Application Nos. 11/134631 and 11/134632. As the rejections are provisional, Applicant declines to provide amendments and arguments at this time.

Based on the above, Applicants respectfully submit that the claims of the present invention are in proper for allowance.

Application No: 10/630,348
Examiner: MERCIER, MELISA S

Favorable consideration and early allowance are therefore respectfully requested and earnestly solicited.

Respectfully Submitted,

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and the mixture is granulated with a solvent mixture of acetone and methylene chloride and then dried. The granules are sized.

Kindly amend paragraph [118] to recite:

77.76% w/w of sodium valproate is mixed 7.78% w/w of ~~Eudragit RS~~ EUDRAGIT RS® (Ammonio Methacrylate Copolymer type B USP) and the mixture is granulated with a solvent mixture of acetone and methylene chloride and then dried. The granules are sized and mixed with 13.6% w/w of hydrogenated castor oil and 0.86% w/w of magnesium stearate.

Kindly amend paragraph [123] to recite:

77.76% w/w of niacin is mixed with 7.78% w/w of ~~Eudragit RS~~ EUDRAGIT RS® (Ammonio Methacrylate Copolymer type B USP) and the mixture is granulated with a solvent mixture of acetone and methylene chloride and then dried. The granules are sized and mixed with 13.6% w/w of hydrogenated castor oil and 0.86% w/w of magnesium stearate.

Kindly amend paragraph [128] to recite:

A) Micro matrix particles--80.93% w/w of venlafaxine hydrochloride is mixed with 19.07% w/w of ~~Eudragit RS~~ EUDRAGIT RS® (Ammonio Methacrylate Copolymer type B USP) and the mixture is granulated with a solvent mixture of acetone and methylene chloride and then dried. The granules are sized.

Kindly amend paragraph [132] to recite:

A) Micro matrix particles--95.24% w/w of niacin is mixed with 4.76% w/w of ~~Eudragit RS~~ EUDRAGIT RS® (Ammonio Methacrylate Copolymer type B USP)